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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,953	09/27/2000	Claude Meares	2307O-099120US	8313

20350 7590 05/01/2002

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 05/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,953	MEARES ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10,11,14-25 and 30-41* is/are pending in the application.

4a) Of the above claim(s) *39-41* is/are withdrawn from consideration.

5)☒ Claim(s) *10 and 11* is/are allowed.

6)☒ Claim(s) *1-3,14-25 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-3, 10-11, 14-25, and 30-38, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that "the claims are drawn to composition and methods that emerge from a common idea or inventive concept and, thus, there is unity of invention" (see page 2 of response). This is not persuasive. As stated in the previous Office Action the Groups are distinct because of divergent subject matter and different classes and subclasses requiring different searches. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**. SU 5/1/02

2. Claims 39-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

3. Claims 4-9, 12-13, 26-29 have been canceled.

4. Claims 1-3, 10-11, 14-25, 30-38 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because on page 1, lines 19-20 contains embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 14-25, 30-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-3, 14-25, 30-38 are indefinite for reciting "in a position proximate" in claims 1 and 25 because the exact meaning of the phrase is not clear. The term is not defined in the specification. Does the phrase mean proximate in a linear amino acid sequence or in three dimensional space? In addition what are the boundaries that encompass "proximate"? What is the distance from a CDR that is encompassed? It is unclear what the meets and bounds are for the term "proximate".

b. Claims 18-19 are indefinite for reciting "L is a chemical bond or linking group that may contain one or more sites" in claim 18 because the exact meaning of the phrase is not clear. It is not clear what the "sites" are or what they are for. Does the term mean a location, a functional group for chemical coupling, or some other meaning?

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 14 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of CHA255 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would

require undue experimentation to reproduce the claimed antibody species CHA255. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

10. Claims 1-3, 14-25, 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant antibody that comprises a reactive site not present in the wild type parent antibody wherein the mutant antibody

comprises 6 CDRs and specifically binds to a metal chelate wherein the reactive site is in a position proximate to or within a CDR, does not reasonably provide enablement for a mutant antibody that does not comprise a full set of 6 CDRs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody that comprises a complementary-determining region that specifically binds to a metal chelate. The claims encompass an antibody that does not contain a full set of 6 CDRs that are required for binding. The specification teaches "CDR" as a "complementarity-determining region" (see page 9, lines 9-10). The specification teaches an antibody which has been engineered to contain a cysteine residue at position 95 and 96 in the light chain of a CHA255 antibody which bind a metal chelate. The specification does not enable an antibody as broadly claimed which can have a single CDR and which is claimed to bind a metal chelate.

Antibodies are made up of CDRs and it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an antibody as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce

the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al and in view of the lack of guidance in the specification and in view of the broadly claimed invention, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-3, 14, 16-19, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Stickney et al (Cancer Research 51:6650-6655, 1991, IDS #7).

The claims recite a mutant antibody comprising a reactive site that is a SH group of cysteine residue in a position proximate to a CDR that is not present in the wild-type antibody wherein the antibody binds a metal chelate and is CHA255, wherein the antibody is bifunctional and binds a cell surface antigen and the antibody has the structure of Ab-L-T and pharmaceutical compositions comprising such.

Strickney et al teach a bifunctional antibody which binds a metal chelate and a cell surface antigen. The antibody that binds the chelate is CHA255. Strickney et al

teach a reactive group of an SH group that is not present in the wild type antibody. The wild type antibody has a disulfide bond. Strickney et al also teach the antibody and a linker and a targeting moiety (see Figure 1). Strickney et al also teach pharmaceutical compositions comprising the bifunctional antibody (see page 6652, Clinical protocol). Due to the broad interpretation of a reactive site and a position proximate to a CDR, the art of Strickney et al reads on the claims because the sulfhydryl groups of the antibody are not present in the wild type and because the term "proximate" is interpreted in its broadest sense to mean anywhere in an antibody, the art of Strickney reads on the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-3, 14, 16, 17, 18, 19, 20, 22, 23, 25, 30, 31, 32, 33, 34, 37, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reardan et al (Nature 316:265-267, 1985, IDS #7) and further in view of Orlandi et al (Proc. Natl. Acad. Sci. USA 86:3833-3837, 1989) and Pastan et al (U.S. Patent 5,747,654, issued 5/5/98, IDS #8) and Goodwin et al (The Journal of nuclear medicine 29:226-234, 1988, IDS #7).

The claims recite a mutant antibody comprising a reactive site that is a cysteine residue in a position proximate to a CDR that is not present in the wild-type antibody wherein the antibody binds a metal chelate and is CHA255 and is a polyaminocarboxylate chelate of a transition metal ion and the chelate comprises a reactive group of complementary reactivity to the SH group wherein the reactive site is an acrylamido moiety, and wherein the mutant antibody further comprises a targeting moiety in the form of Ab-L-T and is bifunctional and compositions comprising such.

Reardan et al teach antibodies to metal chelates and specifically the CHA255 antibody and a hybridoma that produces the antibody. Reardan et al does not teach an

antibody comprising a reactive site that is not in the wild-type antibody or a bispecific antibody to a cell surface antigen or a chelate that is a polyaminocarboxylate. This deficiency is made up for in the teachings of Orlandi et al, Pastan et al, and Goodwin et al.

Orlandi et al teach a method of cloning the variable domains of an antibody from the hybridoma that produces the antibody.

Pastan et al teach a method of stabilizing an antibody by producing an antibody that has a cysteine group at a position proximate to a CDR (see column 2, lines 5-35) in the VL and VH. Pastan et al also teach methods of treatment and the peptides should be free of endotoxin for pharmaceutical purposes (column 8, lines 39-41). The antibody can be directed to a cell surface antigen (see column 11, lines 2-3) and the antibody can be bivalent and bifunctional (see column 7, lines 24-35 and column 9, lines 39-44).

Goodwin et al teach antibodies directed to metal chelates, specifically to a polyaminocarboxylate of Co (see figure 1) and a reactive group that is a SH group or an acrylamido moiety on the chelate.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used a metal chelate antibody of Reardan et al and Goodwin et al and obtain the nucleotide and protein sequence of the VH and the VL as taught by Orlandi et al and produce a disulfide stabilized antibody as taught by Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the metal chelate antibody of Reardan

et al and Goodwin et al and obtain the nucleotide and protein sequence of the VH and the VL as taught by Orlandi et al and produce a disulfide stabilized antibody as taught by Pastan et al because Reardan et al teach an antibody to metal chelates can be used for immunochemical techniques and "Extention of the present work to prepare monoclonal antibodies with dual antigen specificity, which could simultaneously bind a metal chelate and a physiological antigen, may provide further improvements" (see page 267, second to last paragraph, right side of page). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the metal chelate antibody of Reardan et al and Goodwin et al and obtain the nucleotide and protein sequence of the VH and the VL as taught by Orlandi et al and produce a disulfide stabilized antibody as taught by Pastan et al because Pastan et al teach the methods with the nucleic acid sequence of an antibody (which is obvious to obtain by the method of Orlandi et al) and the method is universal to any antibody because the stabilized disulfide bond is produced in a conserved region of the Fv (see column 2, lines 40-45) and the method can be used for bivalent and multivalent construct using a linker (see column 7, lines 28-31). In addition it would have been obvious to one of ordinary skill in the art to make antibodies to other chelates such as polyaminocarboxylates as taught by Goodwin et al because the method of Goodwin is suited for short lived radionuclides (see page 227) and Reardan et al teach that the methods used here can be used for a variety of metal chelates (see page 266, right column, last paragraph). Because Goodwin et al teach compound A and C which would bind to the antibody and it contains a reactive SH and an acrylamido moiety, the art

reads on the claim. Claims 17 and 31 are interpreted to mean the targeting moiety can be the same as the antibody. Due to the broad interpretation of a reactive site and a position proximate to a CDR, the art of reads on the claims. The claims recite a reactive site which is interpreted to be a site where a chemical reaction took place. Because the term "proximate" is interpreted in its broadest sense to mean a site in the antibody, the art reads on the claims.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. Claims 10 and 11 are in condition for allowance.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879